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Ifosfamide-induced Fanconi Syndrome and Desmopressin-responsive Nephrogenic Diabetes Insipidus

To the Editor:

Polyuria, defined as daily urine output exceeding 3 L, is a frequently encountered clinical problem. Water-driven polyuric states are often the result of primary (psychogenic) polydipsia or diabetes insipidus (central or nephrogenic forms).[1] Ifosfamide, a nitrogen mustard alkylating chemotherapeutic agent, is a common cause of renal proximal tubular dysfunction, and has been infrequently associated with the development of polyuria due to an acquired nephrogenic diabetes insipidus state.[2] Nephrogenic diabetes insipidus is characterized by the failure of the renal collecting duct to respond appropriately to secreted antidiuretic hormone (ADH or arginine vasopressin), resulting in the failure to reabsorb luminal water and the inability to concentrate urine.

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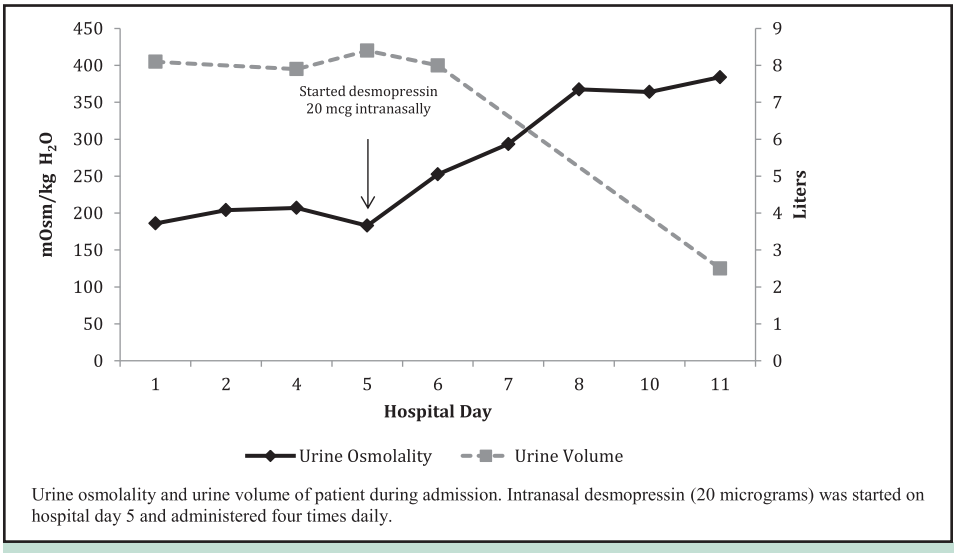
The objective of this study was to report a previously unrecognized treatment strategy for management of nephrogenic diabetes insipidus using intranasal desmopressin.

CASE REPORT

A 26-year-old woman with a history of right pterygoid fossa rhabdomyosarcoma, recurrent and metastatic to the lungs, was hospitalized 10 days after receiving a cumulative dose of 23.4 g/m^2 of ifosfamide for management of weakness, polydipsia, polyuria, fever, hypovolemia, and pancytopenia. Abnormal physical findings included generalized alopecia, low jugular venous pressure, scaphoid abdomen, and decreased skin turgor. Admission laboratory studies were significant for serum sodium 144 mmol/L (normal, 135-145 mmol/L), potassium 3.2 mmol/L (normal, 3.4-4.8 mmol/L), chloride 122 mmol/L (normal, 100-108 mmol/L), bicarbonate 13 mmol/L (normal, 23-31.9 mmol/L), creatinine 123.7 μmol/L (1.4 mg/dL, normal 0.6-1.5 mg/dL [53.0-132.6 μmol/L]), glucose 5.22 mmol/L (94 mg/dL, normal 70-110 mg/dL [3.89-6.10 mmol/L]), phosphorus 0.74 mmol/L (2.3 mg/dL, normal 2.6-4.5 mg/dL [0.8-1.5 mmol/L]), urine osmolality of 186 mOsm/Kg H_2O, and daily urine output of 8.1 L. These abnormalities were consistent with Fanconi syndrome (hypokalemia, hypophosphatemia, hypouricemia, normal gap hyperchloremic metabolic acidosis [venous blood gas pH 7.28, venous pCO_2 32 mm Hg], fractional excretion of bicarbonate >15%, and normoglycemic



Urine osmolality and urine volume of patient during admission. Intranasal desmopressin (20 micrograms) was started on hospital day 5 and administered four times daily.

Figure Response of urine osmolality and urine volume to desmopressin in patient with nephrogenic diabetes insipidus.

glucosuria) and nephrogenic diabetes insipidus, as evidenced by a urine osmolality/plasma osmolality ratio <1.5 that failed to increase following a water deprivation test and one trial of nasal desmopressin insufflation. Administration of repeated doses of desmopressin led to a steady increase in urine osmolality and decrease in urine volume (**Figure**). The patient improved and was discharged on oral electrolyte supplements and intranasal desmopressin. Her nephrogenic diabetes insipidus resolved within 2 weeks, but therapy for Fanconi syndrome persisted.

DISCUSSION

Since its early description in 1972,[2] the concomitant development of Fanconi syndrome and impaired renal concentrating ability (nephrogenic diabetes insipidus) caused by ifosfamide has been rarely reported. Predisposing factors include exposure to high cumulative doses of ifosfamide, overt Fanconi syndrome, and patients younger than 16 years of age.[3]

We report a previously unrecognized therapeutic aspect; that is, the response of the polyuric state to repetitive doses of intranasal desmopressin. Mechanisms involved in ifosfamide-induced impaired distal tubular acidification or concentration defects remain unknown. Our patient's desmopressin responsiveness suggests a partial down-modulation of the basolateral arginine vasopressin receptor 2 (AVPR2), a phenomenon similarly reported in cases of partial nephrogenic diabetes insipidus due to congenital mutations in the AVPR2 gene.[4] Of note, proximal tubular cell uptake of ifosfamide appears to be mediated by human organic cation transporter 2.

Aggressive supportive care should be employed in ifosfamide-induced nephrotoxicity. Given our patient's response to desmopressin, distal tubular dysfunction is reversible, and desmopressin should be considered as part of the treatment to prevent severe volume depletion.

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